

Multiple Myeloma Research Review™

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Issue 26 – 2018

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Abbreviations used in this issue

HIV = human immunodeficiency virus
HR = hazard ratio
MM = multiple myeloma
OS = overall survival
PFS = progression-free survival
SCT = stem-cell transplantation

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Welcome to issue 26 of Multiple Myeloma Research Review.

Two papers reporting trials evaluating selective nuclear export inhibition with selinexor in patients with relapsed or refractory MM begin this issue. Interesting research has found that the HIV antiviral agents nelfinavir and lopinavir were able to reverse carfilzomib resistance due to ABCB1/MDR1 overexpression in MM.

Papers reporting real-world outcomes in MM have also been selected, including trends in Sweden for patients diagnosed between 2008 and 2015, and, to conclude this issue, post-transplant maintenance with lenalidomide or bortezomib versus no maintenance.

We hope you find these and the other selected papers as interesting as we have, and we look forward to reading any comments or feedback you may wish to send.

Kind regards,

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Safety and efficacy of selinexor in relapsed or refractory multiple myeloma and Waldenström macroglobulinemia

Authors: Chen C et al.

Summary: Twenty-two patients with heavily pretreated MM and three with Waldenström's macroglobulinaemia received selinexor 3–60 mg/m² as eight or ten doses per 28-day cycle in the dose-escalation phase of this phase 1 trial, and then in the trial's dose-expansion phase, 59 patients with MM received selinexor 45 mg/m² or 60 mg/m² with dexamethasone 20mg twice weekly in 28-day cycles, or flat doses of selinexor 40mg or 60mg (without corticosteroids) in 21-day cycles. The most common nonhaematological (mostly grade 1–2) adverse events were nausea (75%), fatigue (70%), anorexia (64%), vomiting (43%), bodyweight loss (32%) and diarrhoea (32%), and the most common grade 3–4 adverse events were haematological events, particularly thrombocytopenia (45%). The respective objective response and clinical benefit rates with selinexor on its own were 4% and 21%. The objective response rate increased when dexamethasone was added, with a rate of 50%, and all responses of partial response or better occurred with selinexor 45 mg/m² plus dexamethasone. Furthermore, MM markers decreased from baseline levels in 46% of all participants.

Comment (DS): Selinexor is a first-in-class inhibitor of the nuclear export protein XPO1, which is responsible for delivering tumour suppressor proteins to the cytoplasm of malignant cells; in addition it inhibits egress of glucocorticoid receptors. Blocking XPO1 results in apoptosis of malignant cells. This makes it an appealing option for patients who have failed other approaches. In myeloma, the bortezomib, lenalidomide and carfilzomib failures are a group who need a novel option. The single-agent activity was poor, but when steroids were added the response improved to a more respectable level. The side effects are mostly GI and grade 1–2, but thrombocytopenia is also an issue, especially in those with poor marrow reserve.

Reference: *Blood* 2018;131:855–63

[Abstract](#)

Independent commentary by Dr Ken Romeril, FRACP, FRCPA Haematologist specialising in malignant haematology, Wellington Hospital. He trained in Christchurch, Sydney and Southampton, and is currently at the Wellington Blood and Cancer Centre and Aotea Laboratory. Ken has a particular interest in translational myeloma research and genetics. He is involved in clinical trials, is the current Chair of Myeloma New Zealand and a former chair of the ALLG Myeloma Sub-Committee.



Independent commentary by Dr David Simpson, MBChB, FRACP, FRCPA, Consultant Haematologist North Shore Hospital. His interests are in malignant haematology. He qualified and specialised in Auckland and had postgraduate training in Vancouver and Toronto. He was Assistant Professor of Bone Marrow Transplant at Rush Cancer Institute in Chicago. He has first authored a number of journal articles, reviews, abstracts, and a textbook chapter. He is active in clinical research. David is also a member of the Pharmacy and Therapeutics Committee at North Shore Hospital and the Tender Subcommittee of PHARMAC.



Multiple Myeloma Research Review

Selective inhibition of nuclear export with oral selinexor for treatment of relapsed or refractory multiple myeloma

Authors: Vogl DT et al.

Summary: Forty-eight patients with myeloma refractory to bortezomib, carfilzomib, lenalidomide and pomalidomide, and 31 who were also refractory to an anti-CD38 antibody, received oral selinexor 80mg and dexamethasone 20mg twice weekly in this phase 2 trial. The overall response rate (primary endpoint) was 21%, with no difference between the quad-refractory and penta-refractory participants (21% and 20%, respectively), and it was 35% in participants with high-risk cytogenetics (t[4;14], t[14;16] and del[17p]). The median response duration was 5 months, with 65% of responders alive at 12 months. The most common grade ≥ 3 adverse events were thrombocytopenia (59%), anaemia (28%), neutropenia (23%), hyponatraemia (22%), leucopenia (15%) and fatigue (15%). The adverse event-related dose interruption rate was 52%, the dose reduction rate was 37%, and the treatment discontinuation rate was 18%.

Comment (DS): This was an impressively heavily pretreated population, with a median of 7 prior regimens; 48 had quad-refractory and 31 had penta-refractory myeloma. To see any response in this population is impressive. The response rate of 21% with a fixed-dose oral regimen is encouraging, especially as the toxicity was modest. With selinexor now available on a compassionate basis in NZ, we need to consider this as an option. Selinexor may find a place in early treatment regimens, although this is now becoming a crowded space.

Reference: *J Clin Oncol* 2018;36:859–66

[Abstract](#)

Improvement in overall survival with carfilzomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma

Authors: Siegel DS et al.

Summary: Final OS data (a key secondary endpoint) and updated safety results were reported in this prespecified analysis of the ASPIRE trial, in which adults with relapsed MM were randomised to receive 28-day cycles of lenalidomide and dexamethasone with (KRd) or without (Rd) carfilzomib until withdrawal of consent, disease progression or unacceptable toxicity; all participants received Rd only after 18 cycles. Compared with Rd, KRd was associated with longer median OS duration (48.3 vs. 40.4 months; HR 0.79 [95% CI 0.67, 0.95]), with 11.4-month and 6.5-month longer OS durations in participants who had received 1 and ≥ 2 prior lines of therapy, respectively. KRd and Rd were respectively associated with adverse event-related treatment discontinuation rates of 19.9% and 21.5% and grade ≥ 3 adverse event rates of 87.0% and 83.3% including acute renal failure (3.8% and 3.3%), cardiac failure (4.3% and 2.1%), ischaemic heart disease (3.8% and 2.3%), hypertension (6.4% and 2.3%), haematopoietic thrombocytopenia (20.2% and 14.9%) and peripheral neuropathy (2.8% and 3.1%).

Comment (DS): This update of the ASPIRE study shows that adding carfilzomib to lenalidomide and dexamethasone not only improves PFS, it significantly improves survival, with the median survival extended by 8 months. The patients who received this as second-line therapy had the greatest benefit, with the survival improving by nearly 1 year. In NZ, we should not feel comfortable giving patients lenalidomide and dexamethasone alone now that we know this.

Reference: *J Clin Oncol* 2018;36:728–34

[Abstract](#)



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Carfilzomib resistance due to ABCB1/MDR1 overexpression is overcome by nelfinavir and lopinavir in multiple myeloma

Authors: Besse A et al.

Summary: Pharmacological targeting of ABCB1 has been shown to improve outcomes in MM, but is associated with adverse drug effects and insufficient plasma concentrations. Proteomics analysis has also revealed overexpression of ABCB1 as the most significant change in carfilzomib-resistant MM cells. These researchers studied this overexpression and found that peripheral blood malignant plasma cells exhibited significant upregulation of ABCB1 compared with patients' bone marrow plasma cells. In contrast to bortezomib, ABCB1 overexpression reduced carfilzomib's proteasome-inhibiting activity due to drug efflux, and the cytotoxicity of established drugs for treating MM was significantly reduced in ABCB1-expressing MM cells. In an effort to identify potential drugs to target ABCB1, the researchers identified nelfinavir and lopinavir as potent functional modulators of ABCB1-mediated drug export. They found that these protease inhibitors were able to restore carfilzomib activity at therapeutically relevant drug concentrations, and recommended testing in clinical trials.

Comment (DS): Myeloma patients who fail carfilzomib are usually in trouble. These preclinical data have shown that a common reason for carfilzomib resistance is increased expression of the P-glycoprotein ABCB1. In a series of experiments, removing the gene with CRISPR or inhibiting it with drugs restored carfilzomib sensitivity. The most potent drugs were the HIV antiviral drugs nelfinavir and lopinavir. Unfortunately, in NZ nelfinavir is delisted by Medsafe, but lopinavir is available. Interestingly, nelfinavir was shown to restore bortezomib sensitivity by inhibiting the unfolded protein response, although this paper shows that in contrast to carfilzomib, ABCB1 is not used for bortezomib export. The addition of inhibitors may restore carfilzomib sensitivity long enough for the next new drug to arrive.

Reference: *Leukemia* 2018;32:391–401

[Abstract](#)

Ibrutinib alone or with dexamethasone for relapsed or relapsed and refractory multiple myeloma

Authors: Richardson PG et al.

Summary: In this phase 2 trial, 92 patients who had received ≥ 2 prior lines of therapy, including an immunomodulatory agent, received various doses of ibrutinib with or without weekly dexamethasone 40mg in four cohorts using a Simon 2-stage design. Ibrutinib 840mg plus dexamethasone (n=43) produced the highest clinical benefit rate at 28%, with median duration of 9.2 months, and a PFS duration of 4.6 months. Grade 3–4 haematological adverse events included anaemia in 16% of participants, thrombocytopenia in 11% and neutropenia in 2%, and grade 3–4 nonhaematological adverse events included pneumonia in 7%, syncope in 3% and urinary tract infection in 3%.

Comment (DS): Ibrutinib blocks Bruton's tyrosine kinase, a critical step in B-cell signalling, important for survival, proliferation and adhesion, so it is natural to assess its efficacy in myeloma. The best clinical benefit rate (at least a minor response) of 28% was seen with ibrutinib at 840mg and weekly dexamethasone 40mg; there was little response on monotherapy or with 560mg of ibrutinib with dexamethasone. This is a modest response. In CLL and low-grade lymphomas, drugs that target this pathway have limited effects on bone marrow disease, and similar mechanisms may be at play with myeloma. The results of this study can be seen as half full or half empty, and I am inclined to think there are better agents in development. There may be myeloma subtypes that benefit, perhaps t(11;14) myeloma, which can have a more lymphoid phenotype and was more prevalent in the cohort that received ibrutinib 840mg plus dexamethasone, but venetoclax has already established a niche for this entity.

Reference: *Br J Haematol* 2018;180:821–30

[Abstract](#)



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Look forward again



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For more information, please go to <http://www.medsafe.govt.nz>

Outcome and survival of myeloma patients diagnosed 2008–2015

Authors: Blimark CH et al.

Summary: Data from 4904 patients (72% aged ≥ 65 years at baseline) with MM from the prospective, population-based Swedish Myeloma Registry were reported. The patients were diagnosed over the 8-year period starting in 2008, when the registry was established. During the study period, treatment was guided by the British/Nordic treatment programme (2005) and the Swedish 2010 National Guidelines (updated in 2013). One-year follow-up data were available for 3558 patients with symptomatic disease. The age-adjusted incidence of myeloma was 6.8 cases per 100,000 inhabitants per year. Of the 3998 patients who were initially symptomatic, 77% had osteolytic lesions or compression fractures, 49% had anaemia, 18% had impaired kidney function and 13% had hypercalcaemia. Treatment was high-dose therapy with autologous SCT in 77% and 22% of patients aged ≤ 65 and 66–70 years, respectively. First-line therapy included bortezomib, thalidomide and/or lenalidomide in 31% in 2008, and this increased to 81% in 2014. The respective median relative survival durations of patients aged ≤ 65 and ≥ 66 years with active disease were 7.7 and 3.4 years. Patients with more recent myeloma diagnoses had significantly higher complete response and very good partial response rates, with a greater chance of survival. Patients treated at university hospitals also had a small but significant survival advantage.

Comment (KR): This is a detailed analysis of nearly 500 patients treated in Sweden and the incidence of 6.8 per 100,000 is slightly lower than in NZ, which is currently around 8.0 per 100,000. However, the preponderance of patients over the age of 65 years is higher than in NZ, and illustrates the burden of disease in the older population. They did manage to improve on the low intervention rate of autologous transplantation that is beginning to emerge from local data. The improvement in survival is significant indicating the impact that novel agents are having on real-world studies. The capture of data from a single registry is something that NZ should endeavour to replicate.

Reference: *Haematologica* 2018;103:506–13
[Abstract](#)



Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma

Authors: Raje N et al.

Summary: Adults with newly diagnosed MM (n=1718) who had ≥ 1 lytic bone lesion were randomised to receive subcutaneous denosumab 120mg or intravenous zoledronic acid 4mg every 4 weeks in this phase 3 trial; placebos were administered to achieve blinding, and all participants received first-line antimyeloma therapy. Denosumab was noninferior to zoledronic acid for the primary endpoint of time to first skeletal-related event (HR 0.98 [p=0.010 for noninferiority]). Notable grade 3 \geq adverse events included pneumonia (the most common serious adverse event in both groups), neutropenia, thrombocytopenia and anaemia, but the rates did not vary significantly between the two treatment groups, nor did the incidence of osteonecrosis of the jaw. There was one treatment-related death due to cardiac arrest in the zoledronic acid group.

Comment (KR): This study has been in gestation for some time, as accrual was difficult and the enrolment criteria were challenging from personal experience. The rate of osteonecrosis of the jaw was similar in both groups, which was interesting. Cost will be an issue if denosumab ever gets into the clinic and will be best used in the context of renal impairment.

Reference: *Lancet Oncol* 2018;19:370–81
[Abstract](#)

Bortezomib before and after high-dose therapy in myeloma

Authors: Goldschmidt H et al.

Summary: Long-term follow-up regarding second primary malignancies was reported from the phase 3 HOVON-65/GMMG-HD4 trial, which randomised 613 participants to receive induction VAD (vincristine, doxorubicin, dexamethasone) followed by melphalan 200 mg/m² and autologous SCT and maintenance with thalidomide 50mg daily for 2 years or PAD (bortezomib, doxorubicin, dexamethasone) followed by high-dose melphalan and autologous SCT and maintenance with bortezomib 1.3 mg/m² every 2 weeks for 2 years. At 96 months median follow-up, the PAD arm had significantly longer PFS than the VAD arm (HR 0.76 [95% CI 0.65, 0.89]), but there was no significant difference for OS (0.89 [0.74, 1.08]) or the incidence of second primary malignancies (7% in each arm [p=0.73]). At long-term follow-up, there continued to be abrogation of the negative prognostic effects on PFS and OS of cytogenetic aberration deletion 17p13 and renal impairment at baseline (serum creatinine >2 mg/dL) in the PAD arm.

Comment (KR): These results are a little surprising in that although PFS was improved in the PAD arm, the OS was similar in the two arms. As expected the use of bortezomib was positive in the context of high-risk cytogenetics and renal impairment.

Reference: *Leukemia* 2018;32:383–90
[Abstract](#)

Outcomes of maintenance therapy with lenalidomide or bortezomib in multiple myeloma in the setting of early autologous stem cell transplantation

Authors: Chakraborty R et al.

Summary: Outcomes were reported for 577 patients with newly diagnosed MM who had undergone early autologous transplantation, of whom 341 received no maintenance, 132 received lenalidomide and 104 received bortezomib. Compared with patients who received no maintenance, those who received lenalidomide or bortezomib had higher incidences of high-risk cytogenetics (31% and 58%, respectively, vs. 8% [p<0.001]). Median PFS duration was longer among lenalidomide maintenance recipients compared with no maintenance (37 vs. 28 months; adjusted HR 0.48 [95% CI 0.35, 0.66]), including in subgroups with ISS stage III disease (40 vs. 24 months [p=0.008]) and high-risk cytogenetics (27 vs. 16 months [p=0.032]); median PFS duration with bortezomib maintenance was longer only in the high-risk cytogenetic subgroup (28 vs. 16 months [p=0.035]). Toxicity-related discontinuation rates for lenalidomide and bortezomib maintenance were 17% and 7%, respectively.

Comment (KR): This paper from the Mayo Clinic gives us some extra information over and above the trial data. Maintenance therapy has really become the standard of care in the US and does improve PFS with both drugs. The results in this study are confounded by the use of maintenance in the high-risk cytogenetic group. Bortezomib significantly improved PFS in this group and is now a common theme in many studies. The 17% discontinuation in the lenalidomide group was higher than expected, and maybe use of lower doses may have helped patients stay on the medication.

Reference: *Leukemia* 2018;32:712–8
[Abstract](#)